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Is breast cancer a civilization disease? Common components of type 2 diabetes and breast cancer

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Abstract:

Diabetes Mellitus is one of the most common civilization diseases.The incidence of this disease has been increasing over the last few decades. Research is still being conducted to show the relationship between diabetes and other diseases. Based on these studies, it can be concluded that it also plays a role in the development of cancer. In this review, we focus on analyzing studies on the relationship between type 2 diabetes and breast cancer. We show the influence of diabetes components on the pathomechanism of breast cancer development. We focus on hyperinsulinemia, inflammatory processes, oxidative stress, and obesity, which often accompany type 2 diabetes. Based on the analyzed studies, it can be concluded that type 2 diabetes is a significant factor contributing to cancerous processes associated with breast cancer. In this review, we used articles available in the PubMed database.

Keywords: Diabetes Mellitus, Hyperinsulinism, Breast Cancer

Conflict of interest statement
The authors declare no competing interests.

Introduction:

Diabetes is one of the most common metabolic diseases. In the last 30 years, the number of cases has increased four times [1]. There are two types of diabetes. Type 1 diabetes is an autoimmune disease that manifests in childhood. Its symptoms include increased thirst, frequent urination, nocturia, fatigue, and recurrent infections. Type 2 diabetes is an acquired disease in which there is resistance of the body's cells to insulin and insulin deficiency. Diabetes Mellitus is classified as a civilization disease because it is increasingly common, and lifestyle factors contribute to its onset. Lack of physical activity, unhealthy diet, and obesity are factors that promote the development of type 2 diabetes. It occurs more frequently than type 1 diabetes. Diabetes is a disease that affects life-long. It can lead to various organ complications such as cardiovascular disease [2].

Breast cancer is the most common malignant tumor in women, accounting for 31% of all cases of cancer in women [3]. Its etiology is related to early onset of menstruation and late menopause, obesity, and genetic factors. It may be dependent on estrogens. Their production can be increased by medication, food, and diet. Estrogens are produced in adipose tissue, so obesity contributes to their increased levels. Breast cancer may manifest as a palpable lump, skin changes on the breast, nipple retraction, nipple discharge, and pain. The main diagnostic methods include regular self-examination, ultrasound, and mammography.

Review:

Based on the searched articles, there is a relationship between type 2 diabetes and the risk of breast cancer. 15% of breast cancer patients also have type 2 diabetes [4]. Such a relationship may indicate the existence of common components for both diabetes and breast cancer. In this review, we will focus on the most important factors related to the development and treatment of diabetes and their association with the occurrence of breast cancer.

Insulin and IGF-1

Hyperinsulinemia is a factor that disturbs the normal course of many processes in the body. It causes proliferation of cancer cells and abnormal DNA synthesis, which is related to the anabolic action of hyperinsulinemia [5]. Insulin is a hormone produced by pancreatic cells that regulates blood glucose levels. However, the mechanism of its action is more complex. Insulin receptors are present on the surface of cells. Their connection with insulin activates a cascade of signals that result in an increase in the number of

mitochondria, as well as the synthesis of cellular components such as proteins, lipids, and nucleic acids. [6] One possible side effect of insulin action is the proliferation of cancer cells. This mechanism is based on the activation of the PI3K/Akt/mTOR pathway. In the case of an excessive amount of insulin in the body, signaling pathways are activated more frequently, resulting in increased cell proliferation that can lead to the formation of cancer cells. [7]. Insulin also acts on cells through the protein IGF-1, or Insulin-like Growth Factor 1. Insulin acts on the liver, stimulating it to produce IGF-1. [8,9] It also increases the sensitivity of cells to IGF-1, which causes a greater growth-stimulating effect. Excessive IGF-1 can cause increased proliferation of cancer cells. Its level is associated with insulin production, so an excess of this factor occurs in type 2 diabetes. Studies conducted so far have shown that both insulin and IGF-1 are mitogens for breast cancer cells. It means that they contribute to increased proliferation. [10,11,12] In addition, studies have shown that boys with gynecomastia have an increased level of IGF-1. It can be concluded that this protein directly contributes to breast tissue growth. [13]

Inflammation

Diabetes is a disease accompanied by inflammatory processes. This is related to insulin resistance and obesity, which are often associated with type 2 diabetes. [14] According to studies, there is a strong correlation between hyperinsulinemia and low-grade chronic inflammation. Even moderate hyperinsulinemia in animal studies caused inflammation in adipose tissue. [15] Insulin acts on T lymphocytes, which play an important role in inflammatory processes. It reduces the ability of regulatory T lymphocytes to produce IL-10. This, in turn, impairs their ability to inhibit the production of TNF-α in macrophages. [16] Insulin also acts on macrophages, whose role is to detect and destroy pathogens. We can distinguish between M1 macrophages, which produce IL-6, IL-1β and TNF-α, and M2 macrophages, which produce IL-10 and TGF-β. M1 macrophage products are responsible for killing cancer cells. Cytokines produced by M2 macrophages eliminate inflammatory states. [17,18]. Macrophages, in turn, influence insulin secretion and tissue sensitivity to it. [19,20] Studies show that macrophages express components of the insulin cascade. [21] The insulin receptor (Insr) is a membrane protein that initiates a signaling cascade leading to increased glucose uptake by cells when insulin binds to it. Akt2 kinase activates glucose uptake. Mutations in these kinases can lead to insulin resistance. In this situation, macrophages with reduced production of IL-8, IL-1β and TNF-α will predominate. [22] This can lead to the proliferation of cancer cells, as the production of factors that kill abnormal cells will be reduced.

Oxidative stress

Oxidative stress is a process that results in the production of large amounts of reactive oxygen species, or free radicals, in the body. [23] Free radicals can cause damage to cells and tissues. Excessive production of free radicals can lead to the development of many diseases, such as cancer, skin diseases, and neurodegenerative diseases. [24] According to research, diabetes and increased production of free radicals are linked in several mechanisms. One of them is increased production of advanced glycation end products (AGEs) [22]. These are products of the reaction between glucose and proteins. The result of their formation is the production of free radicals and an effect on the activity of pro-inflammatory pathways. Other processes that occur in diabetes include increased glucose flow through polyol pathways and increased activity of hexosamine pathways. All these factors cause excessive production of oxidative stress, which affects the occurrence of diabetes complications and the development of cancer, including breast cancer. Insulin also affects the production of oxygen radicals in the course of diabetes. Hyperinsulinemia changes the P13 kinase signaling pathway, leading to the formation of reactive oxygen species. [25]

Obesity

Obesity is a civilization disease, and the number of people suffering from it is constantly increasing worldwide. [26] Obesity is one of the factors contributing to the development of type 2 diabetes. In this disease, internal organs surrounded by an increased amount of adipose tissue are more susceptible to cancer. This is related to the processes involving fat cells. In adipose tissue, a small amount of estrogens is produced by the process of

aromatization of androgens. Adipose tissue also plays a role in the production of inflammatory cytokines and adipokines. [27] In the context of breast cancer, resistin is an important factor. Studies have shown that its increased level in serum and cancer cells can serve as a marker for breast cancer. [28] This adipokine acts on cancer cells by activating ERM and Stat3 proteins. [29] This process leads to the formation of metastases and the growth of breast cancer cells. Leptin is also an adipokine. According to research, it is important in the pathogenesis of tumors, and the expression of its receptor has been detected in breast cancer. [30] Leptin, like insulin, when combined with its receptor, activates signaling pathways, including MAPK/ERK and PI3K/Akt. It also activates suppressor cytokine signaling pathways. This action of leptin leads to the proliferation of cancer cells. Estrogen produced by fat cells also affects the growth of cancer cells. It acts by binding to ER receptors on the surface of breast gland cells, and then activating MAPK and AKT pathways. This leads to inhibition of apoptosis and increased proliferation. Estrogen also contributes to the stimulation of angiogenesis. This leads to the formation of new blood vessels, which provide the cancer cells with an environment to survive. In such a mechanism, estrogens from adipose tissue contribute to the development of estrogen-dependent breast tumors. ER-positive breast cancer accounts for up to 70% of all cases. [31]

Summary

Although studies are still being conducted to explain the mechanism by which type 2 diabetes affects the proliferation of cancer cells, it can already be concluded that there is a link between this disease and breast cancer. Research shows that the incidence of breast cancer in women with type 2 diabetes is higher than in healthy women. Insulin plays a significant role in the pathomechanism of type 2 diabetes and the proliferation of cancer cells. Similar effects are shown by inflammatory processes, which are intensified in the case of type 2 diabetes. Obesity, which often accompanies type 2 diabetes and is one of the factors that triggers this disease, is also important. The increased amount of adipose tissue causing an increase in estrogen levels is particularly significant in ER-positive breast cancers.

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